- The National Institute for Occupational Safety and Health (NOISH)

2. Larson's Study Counted Single B Reader Reports, and This Error Caused the Data to be Biased, as Shown in Larson's Table 3.

The Larson paper states in Table 2 that 708 have LPT "as seen by at least two B readers". In Table 3 the numbers are increased to 1,060 because of the Larson study's use of unreliable single B reader reports, for which there may have been conflicting readings by one or two other B readers.

In Table 2, the following should have been provided:

- The breakdown of the 708 with LPT as to their Bourbeau et al index scores. How many had "modest" with an index < median score 2.5 and how many had "high" with an index ≥ 2/5 median score?
- How was the median index score determined?
- What is the range and breakdown of the high index scores for LPT?
- Of the 708 with LPT how many had 2 B readers and how many had 3 B readers reporting especially since 1,118 of the x-rays were read by B Reader 3?

In Table 3, for the analysis, 561 have LPT less than or equal to the median of 2.5 and 499 greater than the median 2.5. This makes a total of 1,060 for the analysis. This is an increase of 352 (50%) of the ATSDR Libby participants over the 708 with LPT. The breakdown of the index scores for this group is also missing, so that one is unable to determine the contribution of this group to each of the modest and high groups. We are further informed the 352 "add-ons" had "LPT detected by only one reader". Since all x-rays were read by 2 or 3 B readers, this implies each of the 352 "add-ons" had one or two B readers that did not identify LPT. If Larson had provided this data indicating the number of B readers for each ATSDR Libby participant, one would be able to determine how many of the 352 "add-ons' had 2 B readers indicating LPT was not present. By omitting all of the above data and methodology, this paper becomes very unscientific.

The Larson paper changed from using 2 or 3 B readers to identify a pleural plaque (LPT) to a single B reader. This changed was announced in fine print under Table 3 and never mentioned in the **Methods, Results,** or **Discussion** in the paper. This critical change in methodology makes the paper flawed and unscientific.

3. The Study Fails to Consider B Reader's Significant Findings of Pleural Fat as Required to Be Noted Under ATSDR B Reader Report Form Box "4D.Fat?" and Therefore the Larson Paper is Unscientific and Seriously Flawed

On a PA chest x-ray pleural fat can mimic pleural plaques and one cannot be distinguished from the other, CT scanning is necessary to do this. The adult population of Libby, Montana has an

incidence of obesity of 49%.[3] This obesity compounds the problems of distinguishing pleural plaques from pleural fat on a PA chest x-ray. ATSDR attempted to try to identify pleural fat by putting box "4D.FAT?" on the B reader reporting forms.[4] This portion of the ATSDR form asks B Readers to note observations of pleural fat.

Larson relied upon the ATSDR reporting forms to obtain the index scores reported in their paper. However, the Larson paper fails to consider the B Reader observations of pleural fat, as documented in box "4D.FAT?" because this data from the B reader report forms is not discussed in the paper. The Larson paper fails to consider documenting pleural fat and its influence on the interpretation of the PA chest x-rays by the ATSDR B readers.

- If a B reader identified a pleural plaque(s) on the PA x-ray and checked box "4D.FAT?" was the result considered to be pleural fat and the report omitted from the paper by the authors?

- If the report was counted, then pleural fat was construed in Larson's paper as pleural plaque. This is not accurate.

- Box "4D.FAT?" was not restricted to the oblique x-rays. The Libby Medical Program has examples where a B reader identifies a plaque(s) in 3A, 3B, or 3C, checks no in Box 4C, and then checks box "4D.FAT?" as positive[5 6]. The Larson paper omitted box "4D.FAT?" from the analysis of the B reader reporting forms that determined the index scores. By ignoring box "4D.Fat?" pleural fat was never identified before being incorporated into the Methods and Results of the paper.

The fact that pleural fat was not accounted for in the B reader reports is unscientific and a serious flaw of the paper. In their paper Larson acknowledge "no negative radiographs were deliberately included as controls." This was a significant mistake in the ATSDR study design. The 2000 – 2001 study should have had control chest x-rays from an unexposed population with BMI's that match those in the Libby study. The inclusion of control chest x-rays would clearly show the impact of pleural fat when attempting to identify pleural plaques in this population.

A significant flaw in the methodology employed by the Larson paper is that it failed to distinguish between pleural plaques and pleural fat, such that observed incidences of pleural plaques may well have been nothing other than irrelevant pleural fat. Obesity not only affects the accuracy of distinguishing between pleural plaques and pleural fat but it also has an impact on pulmonary functions testing, causing restrictive changes. The associations between radiographic findings and spirometry in the Larson paper may be nothing more than the effects of obesity in the Libby population and be unrelated to pleural plaques.

For all of these reasons, in conclusion, in view of the scientifically unsound methodology employed by the Larson paper, the SAB should recommend that EPA not rely on this Larson study, in whole or in part, to reach a determination that pleural plaques cause a loss of pulmonary function.

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Attachments

1. Bourbeau et al 1990; Assessment of Pleural Abnormality
2. Larson et al 2012; Table 3
3. Libby Medical Program BMI data 12/31/2010
4. Standard B Reader Forms for Panel Radiologists (BR1, BR2, BR3) from ATSDR study in Libby, Montana, 2000 – 2001
5. ATSDR Libby participant #10774002, B Reader 1 identifies a face on plaque in 3C., 4C. is checked no and 4D.Fat? is checked positive.
6. ATSDR Libby participant #10548802, B Reader 3 identifies an in profile plaque in 3C., 4C. is checked no and 4D.Fat? is checked positive.

Assessment of Pleural Abnormality

High kilovoltage PA chest radiographs were taken in each subject and read into the ILO 1980 International Classification of Radiographs of Pneumoconioses (24) by two NIOSH-certified B readers. For the present study, one reader was selected a priori because a previous study (25) indicated that he achieved better reproducibility for readings of pleural abnormality. The pleura had to be thickened by 2 mm or more for abnormality to be read. Semiquantitative scores were computed for each of three sites: chest wall, costophrenic angle, and diaphragm. The score for chest wall pleural thickening was computed by summing the reading in profile for each site, using the product of the width category a, b, or c (converted to a numerical score of 1, 2, or 3) and the extent category 1, 2, or 3 plus the reading *en face* (using the extent category 1, 2, or 3). Right and left sides were then added together giving a score ranging form zero to 24. Scores of 1 or 2 were given for obliteration of one or both costophrenic angles and of 1 or 2 for thickening of one or both diaphragms. Because a previous study from our laboratory using the same readers suggested that confluent pleural plaques and diffuse thickening could not be reliably distinguished using the criteria stated in the ILO 1980 instructions (25), our readers were instructed to consider diffuse thickening to be present *only* when there was blunting of the costophrenic angle.

Table 3 Odds of restrictive and obstructive spirometry by degree of radiographic pleural abnormality and covariates* (ORs (95% CI))

	Row n	Restriction	Obstruction
DPT†			
Index=0	6341	1	1
0<index ≤ median (3.0)	78	**2.1 (1.1 to 3.8)**	1.9 (0.9 to 3.8)
Index > median	57	**5.6 (2.7 to 11.6)**	1.7 (0.6 to 4.9)
LPT‡			
Index=0	5416	1	1
0<index ≤ median (2.5)	561	1.3 (1.0 to 1.7)	1.0 (0.7 to 1.4)
Index > median	499	**1.9 (1.5 to 2.5)**	0.9 (0.6 to 1.3)

Statistically significant associations are in bold.

*All models control for parenchymal abnormality, age, sex, smoking history, body mass index, exposure group, number of exposure pathways, duration of residence in Libby and shortness of breath.

†Pleural abnormality index calculated by converting in-profile diffuse thickening widths from 'a', 'b' and 'c' to 1, 2 and 3, then multiplying in-profile widths by in-profile extents and adding face-on extents, and summing the result for each hemithorax. Average severity from two or three B readers used. Possible range of severity index: 0—24. The sum of participants with a DPT abnormality index score >0, n=135, is greater than number of participants with DPT presented in table 2 due to counting participants with DPT detected by only one reader.

‡Pleural abnormality index calculated by converting in-profile localised thickening widths from 'a', 'b' and 'c' to 1, 2 and 3, then multiplying in-profile widths by in-profile extents and adding face-on extents, and summing the result for each hemithorax. Average severity from two or three B readers used. Possible range of severity index: 0—24. The sum of participants with an LPT abnormality index score >0, n=1060, is greater than number of participants with LPT presented in table 2 due to counting participants with LPT detected by only one reader.

DPT, diffuse pleural thickening; LPT, localised pleural thickening.

Calculations of Body Mass Index on Applicants and Members of the Libby Medical Program
Updated December 31st, 2010

As of December 31st, 2010, 1581 applicants and members of the LMP have had BMI's calculated. The results are as follows:

BMI 40 or >	93	6%
BMI 30 to 39.9	678	43%
BMI 25 to 29.9	564	36%
BMI ≤ 25	246	15%
Total	**1581**	**100%**

A. OUTCOME FORM FOR CHEST X-RAYS

BR 1

CASE ID [ ][ ][ ][ ][ ][ ][ ][ ]

1A. DATE OF X-RAY [ ][ ] [ ][ ] [ ][ ] MONTH DAY YEAR

1B. FILM QUALITY 1 2 3 U/R — If not Grade 1 give reason:

1C. IS PA FILM COMPLETELY NEGATIVE? Yes ☐ PROCEED TO SECTION 4C No ☐ PROCEED TO SECTION 2

2A. ANY PARENCHYMAL ABNORMALITIES CONSISTENT WITH PNEUMOCONIOSIS? Yes ☐ COMPLETE 2B AND 2C No ☐ PROCEED TO SECTION 3

2B. SMALL OPACITIES

a. SHAPE/SIZE

PRIMARY		SECONDARY	
p	s	p	s
q	t	q	t
r	u	r	u

b. ZONES

R	L

c. PROFUSION

0/-	0/0	0/1
1/0	1/1	1/2
2/1	2/2	2/3
3/2	3/3	3/+

2C. LARGE OPACITIES

SIZE 0 A B C

PROCEED TO SECTION 3

3A. ANY PLEURAL ABNORMALITIES CONSISTENT WITH PNEUMOCONIOSIS? Yes ☐ COMPLETE 3B, 3C AND 3D No ☐ Proceed to Section 4

3B. PLEURAL THICKENING

a. DIAPHRAGM (plaque) SITE 0 R L

b. COSTOPHRENIC ANGLE SITE 0 R L

3C. PLEURAL THICKENING . . . Chest Wall

a. CIRCUMSCRIBED (plaque)

	SITE	0 R			0 L			
IN PROFILE	i. WIDTH	0	A	B	C	0	A	B	C
	ii. EXTENT	0	1	2	3	0	1	2	3
FACE ON	iii. EXTENT	0	1	2	3	0	1	2	3

b. DIFFUSE

	SITE	0 R			0 L			
IN PROFILE	i. WIDTH	0	A	B	C	0	A	B	C
	ii. EXTENT	0	1	2	3	0	1	2	3
FACE ON	iii. EXTENT	0	1	2	3	0	1	2	3

3D. PLEURAL CALCIFICATION

	SITE 0 R	EXTENT			SITE 0 L	EXTENT		
a. DIAPHRAGM	0	1	2	3	0	1	2	3
b. WALL	0	1	2	3	0	1	2	3
c. OTHER SITES	0	1	2	3	0	1	2	3

PROCEED TO SECTION 4

4A. ANY OTHER ABNORMALITIES? Yes ☐ COMPLETE 4B, 4C AND 4D No ☐ PROCEED TO SECTION 4C

4B. OTHER SYMBOLS (OBLIGATORY)

0 ax bu ca cn co cp cv di ef em es fr hi ho id ih kl pi px rp tb

Report items which may be of present clinical significance in this section.

SPECIFY od.

OD _____

4C. OBLIQUE PLEURAL ABNORMALITY Yes ☐ No ☐

RIGHT OBLIQUE 0 R L

LEFT OBLIQUE 0 R L

4D. FAT? ☐ **/OTHER COMMENTS** _____

SHOULD PARTICIPANT SEE A PHYSICIAN BECAUSE OF COMMENTS IN SECTION 4D? Yes ☐ No ☐

Film Reader: JEL

Date of Reading [ ][ ] [ ][ ] [ ][ ] MONTH DAY YEAR

LIBBY COMMUNITY ENVIRONMENTAL HEALTH PROJECT

BR 2

CASE ID [ ][ ][ ][ ][ ][ ][ ][ ]

1A. DATE OF X-RAY [ ][ ] [ ][ ] [ ][ ] MONTH DAY YEAR

1B. FILM QUALITY If not Grade 1 give reason: [1] [2] [3] [U/R]

1C. IS PA FILM COMPLETELY NEGATIVE? Yes [ ] PROCEED TO SECTION 4C No [ ] PROCEED TO SECTION 2

2A. ANY PARENCHYMAL ABNORMALITIES CONSISTENT WITH PNEUMOCONIOSIS? Yes [ ] COMPLETE 2B AND 2C No [ ] PROCEED TO SECTION 3

2B. SMALL OPACITIES

a. SHAPE/SIZE

PRIMARY		SECONDARY	
p	s	p	s
q	t	q	t
r	u	r	u

b. ZONES

R	L

c. PROFUSION

0/-	0/0	0/1
1/0	1/1	1/2
2/1	2/2	2/3
3/2	3/3	3/+

2C. LARGE OPACITIES

SIZE [0] [A] [B] [C]

PROCEED TO SECTION 3

3A. ANY PLEURAL ABNORMALITIES CONSISTENT WITH PNEUMOCONIOSIS? Yes [ ] COMPLETE 3B, 3C AND 3D No [ ] Proceed to Section 4

3B. PLEURAL THICKENING

a. DIAPHRAGM (plaque) SITE [0] [R] [L]

b. COSTOPHRENIC ANGLE SITE [0] [R] [L]

3C. PLEURAL THICKENING . . . Chest Wall

a. CIRCUMSCRIBED (plaque)

	SITE [0] [R]				[0] [L]			
IN PROFILE i. WIDTH	0	A	B	C	0	A	B	C
ii. EXTENT	0	1	2	3	0	1	2	3
FACE ON iii. EXTENT	0	1	2	3	0	1	2	3

b. DIFFUSE

	SITE [0] [R]				[0] [L]			
IN PROFILE i. WIDTH	0	A	B	C	0	A	B	C
ii. EXTENT	0	1	2	3	0	1	2	3
FACE ON iii. EXTENT	0	1	2	3	0	1	2	3

3D. PLEURAL CALCIFICATION

	SITE [0] [R] EXTENT				SITE [0] [L] EXTENT			
a. DIAPHRAGM	0	1	2	3	0	1	2	3
b. WALL	0	1	2	3	0	1	2	3
c. OTHER SITES	0	1	2	3	0	1	2	3

PROCEED TO SECTION 4

4A. ANY OTHER ABNORMALITIES? Yes [ ] COMPLETE 4B, 4C AND 4D No [ ] PROCEED TO SECTION 4C

4B. OTHER SYMBOLS (OBLIGATORY)

[0] [ax] [bu] [ca] [cn] [co] [cp] [cv] [di] [ef] [em] [es] [fr] [hl] [ho] [id] [ih] [kl] [pl] [px] [rp] [tb]

Report items which may be of present clinical significance in this section.

SPECIFY od.

[OD] _____

4C. OBLIQUE PLEURAL ABNORMALITY Yes [ ] No [ ]

RIGHT OBLIQUE [0] [R] [L]

LEFT OBLIQUE [0] [R] [L]

4D. FAT? [ ] /OTHER COMMENTS _____

SHOULD PARTICIPANT SEE A PHYSICIAN BECAUSE OF COMMENTS IN SECTION 4D? Yes [ ] No [ ]

Film Reader: KR

Date of Reading [ ][ ] [ ][ ] [ ][ ] MONTH DAY YEAR

LIBBY COMMUNITY ENVIRONMENTAL HEALTH PROJECT

BR 3

CASE ID [ ][ ][ ][ ][ ][ ][ ][ ]

1A. DATE OF X-RAY [ ][ ] [ ][ ] [ ][ ] MONTH DAY YEAR

1B. FILM QUALITY [1] [2] [3] [U/R] If not Grade 1 give reason:

1C. IS PA FILM COMPLETELY NEGATIVE? Yes [ ] PROCEED TO SECTION 4C No [ ] PROCEED TO SECTION 2

2A. ANY PARENCHYMAL ABNORMALITIES CONSISTENT WITH PNEUMOCONIOSIS? Yes [ ] COMPLETE 2B AND 2C No [ ] PROCEED TO SECTION 3

2B. SMALL OPACITIES

a. SHAPE/SIZE

PRIMARY		SECONDARY	
p	s	p	s
q	t	q	t
r	u	r	u

b. ZONES

R	L

c. PROFUSION

0/-	0/0	0/1
1/0	1/1	1/2
2/1	2/2	2/3
3/2	3/3	3/+

2C. LARGE OPACITIES

SIZE [0] [A] [B] [C]

PROCEED TO SECTION 3

3A. ANY PLEURAL ABNORMALITIES CONSISTENT WITH PNEUMOCONIOSIS? Yes [ ] COMPLETE 3B, 3C AND 3D No [ ] Proceed to Section 4

3B. PLEURAL THICKENING

a. DIAPHRAGM (plaque) SITE [0] [R] [L]

b. COSTOPHRENIC ANGLE SITE [0] [R] [L]

3C. PLEURAL THICKENING . . . Chest Wall

a. CIRCUMSCRIBED (plaque)

	SITE [0] [R]	[0] [L]
IN PROFILE i. WIDTH	[0] [A] [B] [C]	[0] [A] [B] [C]
ii. EXTENT	[0] [1] [2] [3]	[0] [1] [2] [3]
FACE ON iii. EXTENT	[0] [1] [2] [3]	[0] [1] [2] [3]

b. DIFFUSE

	SITE [0] [R]	[0] [L]
IN PROFILE i. WIDTH	[0] [A] [B] [C]	[0] [A] [B] [C]
ii. EXTENT	[0] [1] [2] [3]	[0] [1] [2] [3]
FACE ON iii. EXTENT	[0] [1] [2] [3]	[0] [1] [2] [3]

3D. PLEURAL CALCIFICATION

	SITE [0] [R] EXTENT			
a. DIAPHRAGM	[0]	[1]	[2]	[3]
b. WALL	[0]	[1]	[2]	[3]
c. OTHER SITES	[0]	[1]	[2]	[3]

	SITE [0] [L] EXTENT			
a. DIAPHRAGM	[0]	[1]	[2]	[3]
b. WALL	[0]	[1]	[2]	[3]
c. OTHER SITES	[0]	[1]	[2]	[3]

PROCEED TO SECTION 4

4A. ANY OTHER ABNORMALITIES? Yes [ ] COMPLETE 4B, 4C AND 4D No [ ] PROCEED TO SECTION 4C

4B. OTHER SYMBOLS (OBLIGATORY)

[0] [ax] [bu] [ca] [cn] [co] [cp] [cv] [di] [ef] [em] [es] [fr] [hl] [ho] [id] [ih] [kl] [pi] [px] [tp] [tb]

Report items which may be of present clinical significance in this section.

SPECIFY od.

[OD] _____

4C. OBLIQUE PLEURAL ABNORMALITY Yes [ ] No [ ]

RIGHT OBLIQUE [0] [R] [L]

LEFT OBLIQUE [0] [R] [L]

4D. FAT? [ ] /OTHER COMMENTS _____

SHOULD PARTICIPANT SEE A PHYSICIAN BECAUSE OF COMMENTS IN SECTION 4D? Yes [ ] No [ ]

Film Reader: JEP

Date of Reading [ ][ ] [ ][ ] [ ][ ] MONTH DAY YEAR

LIBBY COMMUNITY ENVIRONMENTAL HEALTH PROJECT

BR 1

CASE ID. 1 0 7 7 4 0 0 2

5877

1A. DATE OF X-RAY 1 0 | 3 0 | 0 0 — MONTH DAY YEAR

1B. FILM QUALITY [X] 1 [ ] 2 [ ] 3 [ ] U/R — If not Grade 1 give reason:

1C. IS PA FILM COMPLETELY NEGATIVE? Yes [ ] PROCEED TO SECTION 4C — No [X] PROCEED TO SECTION 2

2A. ANY PARENCHYMAL ABNORMALITIES CONSISTENT WITH PNEUMOCONIOSIS? Yes [ ] COMPLETE 2B AND 2C — No [X] PROCEED TO SECTION 3

2B. SMALL OPACITIES

a. SHAPE/SIZE — PRIMARY: p s / q t / r u — SECONDARY: p s / q t / r u

b. ZONES — R L

c. PROFUSION — 0/- 0/0 0/1 / 1/0 1/1 1/2 / 2/1 2/2 2/3 / 3/2 3/3 3/+

2C. LARGE OPACITIES SIZE: 0 A B C — PROCEED TO SECTION 3

3A. ANY PLEURAL ABNORMALITIES CONSISTENT WITH PNEUMOCONIOSIS? Yes [X] COMPLETE 3B, 3C AND 3D — No [ ] Proceed to Section 4

3B. PLEURAL THICKENING

a. DIAPHRAGM (plaque) SITE [X] 0 R L

b. COSTOPHRENIC ANGLE SITE [X] 0 R L

3C. PLEURAL THICKENING . . . Chest Wall

a. CIRCUMSCRIBED (plaque)

	Right	Left
SITE	0 [X] R	[X] 0 L
IN PROFILE i. WIDTH	[X] 0 A B C	0 A B C
ii. EXTENT	[X] 0 1 2 3	0 1 2 3
FACE ON iii. EXTENT	0 [X] 1 2 3	0 1 2 3

b. DIFFUSE

	Right	Left
SITE	[X] 0 R	[X] 0 L
IN PROFILE i. WIDTH	0 A B C	0 A B C
ii. EXTENT	0 1 2 3	0 1 2 3
FACE ON iii. EXTENT	0 1 2 3	0 1 2 3

3D. PLEURAL CALCIFICATION

	SITE [X] 0 R — EXTENT	SITE [X] 0 L — EXTENT
a. DIAPHRAGM	0 1 2 3	0 1 2 3
b. WALL	0 1 2 3	0 1 2 3
c. OTHER SITES	0 1 2 3	0 1 2 3

PROCEED TO SECTION 4

4A. ANY OTHER ABNORMALITIES? Yes [X] COMPLETE 4B, 4C AND 4D — No [ ] PROCEED TO SECTION 4C

4B. OTHER SYMBOLS (OBLIGATORY)

0 ax bu ca cn [X] co cp cv di ef em es fr hi ho id ih kl pi px rp tb

Report items which may be of present clinical significance in this section.

SPECIFY od. [ ] OD

4C. OBLIQUE PLEURAL ABNORMALITY Yes [ ] No [X]

RIGHT OBLIQUE 0 R L

LEFT OBLIQUE 0 R L

4D. EAT? [X] /OTHER COMMENTS

- increased cardiac size
- pleural change on (R) above vs plaque.

SHOULD PARTICIPANT SEE A PHYSICIAN BECAUSE OF COMMENTS IN SECTION 4D? Yes [X] No [ ]

Film Reader: JEL

Date of Reading 0 1 | 1 5 | 0 1 — MONTH DAY YEAR

BBY COMMUNITY ENVIRONMENTAL HEALTH PROJECT

BR 3

CASE ID 1 0 5 4 8 8 0 2 2557

1A. DATE OF X-RAY: MONTH 0 8, DAY 1 5, YEAR 0 0

1B. FILM QUALITY: 1 2 3 U/R — If not Grade 1 give reason:

1C. IS PA FILM COMPLETELY NEGATIVE? Yes ☐ PROCEED TO SECTION 4C No ☒ PROCEED TO SECTION 2

2A. ANY PARENCHYMAL ABNORMALITIES CONSISTENT WITH PNEUMOCONIOSIS? Yes ☐ COMPLETE 2B AND 2C No ☒ PROCEED TO SECTION 3

2B. SMALL OPACITIES

a. SHAPE/SIZE

PRIMARY		SECONDARY	
p	s	p	s
q	t	q	t
r	u	r	u

b. ZONES: R L

c. PROFUSION

0/-	0/0	0/1
1/0	1/1	1/2
2/1	2/2	2/3
3/2	3/3	3/+

2C. LARGE OPACITIES

SIZE: 0 A B C

PROCEED TO SECTION 3

3A. ANY PLEURAL ABNORMALITIES CONSISTENT WITH PNEUMOCONIOSIS? Yes ☒ COMPLETE 3B, 3C AND 3D No ☐ Proceed to Section 4

3B. PLEURAL THICKENING

a. DIAPHRAGM (plaque) SITE: 0 R L

b. COSTOPHRENIC ANGLE SITE: 0 R L

3C. PLEURAL THICKENING . . . Chest Wall

a. CIRCUMSCRIBED (plaque)

	SITE: 0 R		SITE: 0 L	
IN PROFILE	0	1	0	1
i. WIDTH	0 A B C		0 A B C	
ii. EXTENT	0 1 2 3		0 1 2 3	
FACE ON				
iii. EXTENT	0 1 2 3		0 1 2 3	

b. DIFFUSE

	SITE: 0 R		SITE: 0 L	
IN PROFILE				
i. WIDTH	0 A B C		0 A B C	
ii. EXTENT	0 1 2 3		0 1 2 3	
FACE ON				
iii. EXTENT	0 1 2 3		0 1 2 3	

3D. PLEURAL CALCIFICATION

	SITE: 0 R — EXTENT				SITE: 0 L — EXTENT			
a. DIAPHRAGM	0	1	2	3	0	1	2	3
b. WALL	0	1	2	3	0	1	2	3
c. OTHER SITES	0	1	2	3	0	1	2	3

PROCEED TO SECTION 4

4A. ANY OTHER ABNORMALITIES? Yes ☐ COMPLETE 4B, 4C AND 4D No ☒ PROCEED TO SECTION 4C

4B. OTHER SYMBOLS (OBLIGATORY)

0 ax bu ca cn co cp cv di ef em es fr hi ho id ih kl pi px rp tb

Report items which may be of present clinical significance in this section.

SPECIFY od.

OD

4C. OBLIQUE PLEURAL ABNORMALITY Yes ☐ No ☒

RIGHT OBLIQUE 0 R L

LEFT OBLIQUE 0 R L

4D. FAT? ☒ /OTHER COMMENTS

SHOULD PARTICIPANT SEE A PHYSICIAN BECAUSE OF COMMENTS IN SECTION 4D? Yes ☐ No ☒

Film Reader: JEP

Date of Reading: MONTH 1 2, DAY 1 6, YEAR 1 1

APPENDIX B – 15

UNIVERSITY OF Cincinnati

Department of Environmental Health
Occupational and Environmental Medicine Division

University of Cincinnati
Academic Health Center
PO Box 670056
Cincinnati, Ohio 45267-0056

Delivery Address:
3223 Eden Avenue
Cincinnati, OH 45267

January 31, 2012

Diana Wong, Ph.D
Designated Federal Officer
Scientific Advisory Board
U.S. EPA

RE: Material for SAB review related to the Draft Toxicological Review of Libby Amphibole Asbestos

Dear Dr. Wong,

Attached please find material for review by the Scientific Advisory Board (SAB) related to the Draft Toxicological Review of Libby Amphibole Asbestos. The file contains information about upcoming analyses/publications related to the Marysville, Ohio cohort. This cohort is instrumental in understanding the health risks associated with Libby amphibole exposure. The SAB may find it useful to be aware of the upcoming availability of this additional research related to this cohort.

Sincerely,

James E. Lockey, MD, MS
Professor-Department of Environmental Medicine
Division of Occupational and Environmental Medicine
Department of Internal Medicine, Pulmonary Division
University of Cincinnati College of Medicine

Status of data collected in 2010-2011 related to the University of Cincinnati pulmonary health study of 513 Marysville, Ohio workers exposed to Libby amphibole

Title/Topic	Content	Status
Exposure estimates for workers in a facility expanding Libby vermiculite: Updated values and comparison to original 1980 values	Methodology utilized to refine the Marysville, Ohio workers exposure matrix and comparison to the exposure matrix used in the 1980 and 2004 epidemiologic studies	Submitted for publication December 2011
Mesothelioma associated with commercial use of vermiculite containing Libby amphibole	SMRs and SRRs used to investigate potential asbestos-related mortality among 136 deceased workers from the Marysville cohort	Submitted for publication December 2011
Chest X-ray and HRCT findings associated with low levels of exposure to Libby amphibole (tentative title)	Cross-sectional analyses evaluating association between cumulative fiber exposure and chest X-rays/HRCTs of 191 Marysville workers as related to pleural and parenchymal changes	In preparation; target to submit Spring 2012
Spirometry, Diffusion, Lung Volume studies	Cross-sectional and longitudinal analyses regarding the potential association between cumulative fiber exposure and spirometry collected in 1980 (n=512), 2004 (n=231), 2010 (n=154), diffusion and lung volume studies from 2010 (n=154) and chest HRCT (n=191)/X-ray (n=305) findings.	Data analysis pending; target to submit Summer/Fall 2012
Autoimmune disease/biomarkers (grant submitted)	Evaluate the potential association between cumulative fiber exposure and autoimmune disease and/or autoimmune biomarkers via serum samples and health questionnaires from 151 members of the Marysville cohort.	Biological sample analyses pending; target to submit Winter 2013

January 26, 2012

APPENDIX B – 16

U.S. EPA's External Review Draft Toxicological Review of Libby Amphibole Asbestos

Presentation for the
Science Advisory Board
6 Feb. 2012

David Bussard,
Director, Washington Division
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency

Overview

- Noncancer Assessment
- Cancer Assessment
- New Publications

Why Assess Libby Amphibole Asbestos Specifically?

- Clear awareness of noncancer effects in those exposed to Libby amphibole and no IRIS value explicitly for noncancer effects of asbestos.
- Opportunity with epidemiology data to study exposures to the material as mined at Libby and processed rather than estimate its risk from its component minerals.

Toxicological Review

- Review of the available scientific literature most relevant to evaluating the potential health hazard posed from exposures to Libby amphibole asbestos (LAA).
- Aware of the broader literature on asbestos generally, but not trying to publish a review of the entire asbestos literature.

Elements of Toxicological Review

- Hazard description.
- Reference Concentration (RfC): "An estimate *(with uncertainty spanning perhaps an order of magnitude)* of a continuous inhalation exposure to the human population *(including sensitive subgroups)* that is likely to be without an appreciable risk of deleterious effects during a lifetime."
- Inhalation Unit Risk (IUR): "An inhalation unit risk (IUR) is typically defined as a plausible upper bound on the estimate of cancer risk per $\mu g/m^3$ air breathed for 70 years." [fibers/cc in this case]

Literature Search in Support of the Libby Amphibole Assessment

- Used search terms for relevant mineral forms:
  - Libby amphibole ("Libby", "Libby asbestos," etc.)
  - Tremolite
  - Winchite
  - Richterite
- Focused additional search on some related issues (e.g. fiber toxicokinetics, susceptible populations, MOA for asbestos in general).
- Drew from a range of literature sources
  - Peer-reviewed journals
  - Government reports
  - Materials submitted to the EPA docket

Section 4: Noncancer Hazard Identification

- Weight of evidence is adequate for:
  - Localized pleural thickening / pleural plaques
  - Diffuse pleural thickening
  - Asbestosis
- Data were insufficient for hazard determination:
  - Other systemic effects

Study Selection Criteria for RfC Quantification

(Table 5-2, Section 5.2.1.1)

- Exposure estimates are available for the study group
- Good study design characteristics
  - Sufficient follow-up
  - Study size / participation rates and no indication of bias
  - Design/analytic approach to address relevant sources of potential confounding
- Relevant exposures
  - Chronic studies versus subchronic or acute
  - Exposure intensity (inform environmental scenarios)
- Good measurements of exposure
  - Measured data (site/task specific)
  - Sample collection / analysis
  - Availability of individual-level exposure data
  - Quality of exposure reconstruction
- Good ascertainment of effects (health outcomes)
  - Severity of effect (precursor, minimal effect, more severe effect)
  - Measurement techniques adequate and sensitive
  - Measurement of effects independent of knowledge of exposure level/group

Two occupational cohorts for RfC Derivation
(Section 5.1)

- Miners in Libby, Montana
  [Amandus et al. (1987 a,b); McDonald et al. (1986b)]
- O. M. Scott workers in Marysville, Ohio
  (vermiculite from Libby, MT)
  [Lockey et al. (1984); Rohs et al. (2008)]

Advantages of O.M. Scott Cohort: (Section 5.2.1.3.2)

- Adequate follow-up
- Minimal exposure outside of the workplace
- Better quality radiographs (ILO 2000, for some)
- Lower exposures – closer to POD
- Ability to consider more covariates

EPA decided to conduct its own exposure-response modeling with individual data

- Published data only presented by exposure quartiles.
- New analysis would allow for explicit evaluation of important covariates.
- ...allow use of the higher quality data (sub-cohort); increasing confidence in the resulting exposure-response relationship.
- ...allow sensitivity analyses

Several Radiological Endpoints Considered
(Section 5.2.1.4)

- Available data for exposure-response modeling was limited to effects as viewed using standard radiographs:
  - Small opacities – asbestosis
  - Costophrenic angle (blunting/obliteration)
  - Pleural thickening
    - Localized pleural thickening (LPT)
    - Diffuse pleural thickening (DPT)

Criteria for Selecting Critical Effect
(applied in Section 5.2.2)

- Adverse itself, a precursor to an adverse effect or a biologic marker for a relevant health effect.
- Confounding can be adequately accounted for.
- Measured with adequate sensitivity for the results to be biologically relevant.
- Adequate data to define an exposure-response relationship (BMDL or LOAEL/NOAEL).

EPA selected localized pleural thickening (LPT)

EPA Has Requested Review of the Exposure Reconstruction (Section 5.2.3.1, Appendix F)

O.M. Scott workers

- Original Job Exposure Matrix (Lockey 1985)
  - No exposure measurements prior to 1972;
  - Engineering controls implemented from 1968 on
  - 235 air samples
- Additional information available for exposure reconstruction
  - 589 new air samples
  - Focus groups
  - Seasonal work schedules

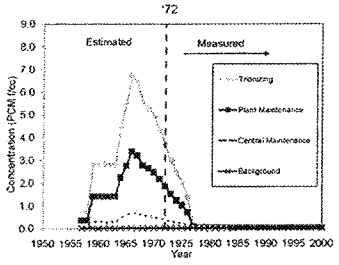


Figure 5-1. Estimated and measured exposure concentrations in Marysville, OH facility

Criteria for selection of the Sub-cohort from O.M. Scott (Marysville, Ohio) (Section 5.2.3.2)

Criteria	Full Cohort	Sub-cohort (limit to those hired after 1971)
Type and Quality of Outcome Assessment (i.e. Radiographs)	Merge 1980 and 2000-2005 exam data	2002-2005 exam data
Quality of exposure data (measured, reconstructed, quality of information for reconstruction)	Missing measured data for pre-1972 exposures. Pre-1972 exposures were reconstructed (Appendix F).	Post-1971 exposure estimates based on measured data
Sample size (statistical power)	N=434, 61 LPT cases	N=118, 12 LPT cases
Data available to address covariates (age, DOB, sex, BMI, smoking, hire date etc.)	Not available for the 1980 cohort (e.g. smoking and BMI)	Lower proportion of missing data (i.e. BMI)
Available endpoints for consideration as the critical effect	LPT, OPT and asbestosis	LPT (only 1 case OPT)
Time to x-ray, from first exposure	Range: (6 mo. to 47 years)	Range: (23.2 to 32.6 years)

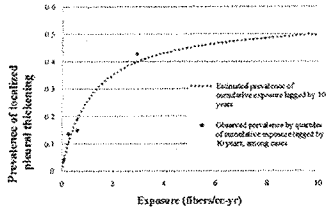
RfC Exposure-Response Modeling

(Section 5.2.3.3, Appendix E)

Best-fitting model was a Michaelis-Menten model

$P(LPT) = background + (Plateau - background) \times CE + [exp(-a) \times CE]$

Benchmark dose software suite of models evaluated.



Graph of observed and estimated prevalence of localized pleural thickening calculated using the Michaelis-Menten model with 10-year lagged exposure.

Reference Concentration (Section 5.2.4)

- Point of Departure: 0.1177 (fibers/cc) × year
  The lower 95th confident interval on exposure causing a 10% LPT response
- Converted to lifetime exposure concentration:
  0.1177÷ (70-10) yrs
  $=1.96 \times 10^{-3}$ fibers/cc
- Uncertainty Factors Applied: Total of 100
  1.96×10^{-3} fibers/cc ÷ 100

RfC $= 2 \times 10^{-5}$ fibers/cc; lifetime exposure

Note: The alternative full cohort model provided a POD of 0.0136 (fibers/cc) × year, where T=40 years. If UF total of 100 were applied that would yield an RfC of 4×10^{-6} fibers/cc for lifetime exposure.

Sensitivity Analyses (Section 5.3.1)

- Limited Quantitative Impact:
  - Sensitivity to background rate of LPT (15%)
  - Sensitivity to lag (50%)
- Smoking status
  - Statistical power is limited, but analysis suggests a POD for smokers might be lower
- Extrapolation to full-lifetime exposures
  - Two alternatives presented
  - PODs vary by a factor of 4
- Choice of critical effect (Table 5-5)
  - As expected, POD for LPT was lower than PODs for DPT and small opacities
  - Limitation of critical effect to bilateral LPT would result in similar POD: 0.1337 vs. 0.1177 (fibers/cc) yrs

Charge asks your advice on key decision points:

Data on which the RfC is based:

- Exposure reconstruction
- Choice of sub-cohort
- Endpoint selection

Quantitative assessment:

- Exposure-response modeling
  - Evaluation of covariates
  - Selection of best-fit model
- Extrapolation to full-lifetime exposures
- Application of uncertainty factors

Section 4: Evaluation of Carcinogenicity

"Carcinogenic to Humans"

- Associated with increased mortality
  - Lung cancer
  - Mesothelioma

Criteria for Study/Dataset Selection

1) All studies of cancer incidence or mortality in people exposed to Libby Amphibole asbestos
2) Excluded studies without quantitative exposure data (community studies)
3) Excluded studies without well-defined populations (case studies)

Libby workers cohort (Sullivan, 2007)

- Cohort study of inhalation exposures of chronic duration
- Well-documented design, methods, and population characteristics
- Could (with researcher, Dr. Sullivan) extend mortality follow-up and conduct individual-level data analysis

Original analysis

Individual-level data allow for more detailed cancer analysis than from using only summary results in the literature.

- Better understanding of important aspects of the job exposure matrix (5.4.3.5)
- Allows explicit control of important covariates (5.4.3.6)
- Allows investigation of various parameterizations of exposure (5.4.2.4)
- Allows accounting for time-varying aspects of exposure (5.4.3.6.2)
- Allows sensitivity analysis of influence of early high exposure intensities (5.4.3.6.4)
- Allows sensitivity analysis of potential confounding by smoking (5.4.3.6.5)

Prior published analyses have sometimes used the full cohort and sometimes sub-cohorts.

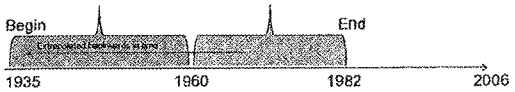
Reference	Cohort definition	Employment Requirement	Mortality Follow-up	Study size (N)
McDonald et al. (1986a and 2004)	Males hired prior to 1963 Exposures 1935-1982	1 year or more	1999	406
Amandus and Wheeler (1987)	Males hired prior to 1970 Exposures 1935-1982	1 year or more	1982	575
Sullivan (2007)	White males still alive post-1959 Exposures 1935-1982	1 day or more	2001	1,672
* Berman and Crump (2008)	White males still alive post-1959 Exposures 1935-1982	1 day or more	2001	1,672
Larson et al. (2010a)	Full cohort Exposures 1938-1993	1 day or more	2006	1,862
* Moolgavkar et al. (2010)	White males still alive post-1959 Exposures 1935-1982	1 day or more	2001	1,662
		1 year or more	2001	801

* Re-analysis of Sullivan (2007)

NIOSH Job Exposure Matrix: important information is missing regarding pre-1960 exposures.

Exposure data extrapolated back in time from late 1960s

Job-specific exposure information with range 1-188 fibers/cc



71% of workers had missing department and job title (706/991) during this time.

Only 1% of workers had missing department and job title (9/880)

EPA identified the sub-cohort hired after 1959 as most appropriate study population.

- Reduces measurement error
- Reduces bias

Variety of Exposure Metrics Evaluated

(Section 5.4.2.5)

- **Responsive to SAB's review of OSWER asbestos modeling.**
- **Allows exploration of the influence of early versus late exposures**
  - CE metric gives equal weight to all exposures
  - Residence-time weighted CE gives relatively greater weight to early exposures
  - Decay (half-lives) gives relatively greater weight to late exposures
- **When also considering lags and decay rates, a suite of 40 different parameterizations of exposure metrics considered:**
  - Lag time to account for cancer latency (0,5,10, 15, or 20 years)
  - Decay of exposure metric (half-life of 5,10, 15, or 20 years)
- **For mesothelioma, the metric proposed by Peto and used by Nicholson in IRIS assessment of asbestos (EPA, 1986a) was also evaluated.**

Cancer Exposure-Response Modeling
(Section 5.4.3.6)

➢**For each kind of cancer modeled, EPA used a model form similar to those in the literature for this cohort.**

- Mesothelioma:
  - Absolute risk model [EPA, 1986a; Moolgavkar et al., 2010]
  - Specifically, a Poisson regression absolute risk model used for rare events (McDonald et al., 2004)
- Lung cancer:
  - Relative risk model [EPA, 1986a; Sullivan, 2007]
  - Specifically, Cox regression relative risk models used for analysis of time-varying exposures [Larson et al., 2010a; Moolgavkar et al., 2010]

➢**Model / exposure metric selection criteria based on relative model fit; then selected health-protective when similar fit.**

Cancer Exposure-Response Results
(Section 5.4.4)

➢**Model / exposure-metric results**

- Mesothelioma:
  - The best-fitting approach had lagged CE with decay (Table 5-11)
  - The metrics that gave more weight to early exposures, such as the Peto model used by Nicholson used in the 1986 IRIS assessment of asbestos (EPA, 1986a) and RTW models, did not fit this data well.
- Lung cancer:
  - Adequate model fit with multiple exposure metrics (Table 5-12)
  - The best-fitting approach had lagged CE with or without decay

Derivation of the Cancer IUR (Section 5.4.5)

1) Point of Departure (POD): (Appendix G)
   - Exposure-response models for each cancer were used to calculate lifetime cancer risk
   - Response: 1% extra risk of mortality for continuous lifetime exposure (central estimate and 95% lower bound)
2) Cancer-specific unit risks were obtained by dividing the extra risk (1%) by the POD (lower bound on risk-specific exposure).
   - Mode of action not established.
   - Linear extrapolation default.

Derivation of the Cancer IUR (Section 5.4.5)

3) Mesothelioma unit risk adjusted to compensate for underascertainment of deaths (Kopylev et al., 2011)
   - Adjustment factor of 1.39 times (39% increase)
4) The cancer-specific unit risk estimates for mortality from mesothelioma and lung cancer separately were then statistically combined to derive the proposed IUR=0.17 per fibers/cc (see Section 5.4.5.3 for combined cancer)

•Comparison with other result shows a very similar estimate of mesothelioma cancer unit risks.

•EPA's central estimate of lung cancer unit risk is higher than that of others using this cohort.

Study	Mesothelioma		Lung Cancer	
	Cases/N	Estimated lifetime risk (per fibers/cc)	Cases/N	Estimated Lifetime risk (per fibers/cc)
EPA (this assessment)	7/880	**Upper Bound = 0.12 Central = 0.08**	32/880	**Upper Bound = 0.068 Central = 0.040**
Sullivan, 2007	15/1,672	(No estimates of absolute risk)	99/1,672	Upper Bound = 0.037 Central = 0.023
Berman and Crump, 2008	19/1,672	(No estimates provided)	93/1,672	Upper Bound = 0.079 Central = 0.027
Moolgavkar et al., 2010	15/1,662	Upper Bound = 0.13 Central = 0.08	95/1,662	Upper Bound = 0.011 Central = 0.009
Larson et al., 2010	19/1,862	(No estimates of absolute risk)	98/1,862	Upper Bound = 0.010 Central = 0.007

Smoking and Lung Cancer (Section 5.4.6)

- **Looked at potential confounding of lung cancer results (Section 5.4.6.1.6).**
  - Restriction to sub-cohort partially limits confounding by smoking
  - Modeling of birth date partially addresses changes in smoking patterns
  - Proportional hazard test did not show changes over time when smoking rates were changing after Surgeon General's report (1964)
- **Method of Richardson (2010) to evaluate confounding by smoking in the absence of data on smoking did not suggest any confounding. (Section 5.4.3.6.5)**
- **Lung cancer results may reflect effect modification (Section 5.4.6.1.7)**
  - Possible that the estimated effect for lung cancer is actually the risk for an interaction between Libby Amphibole asbestos and smoking
  - Would overestimate risk in populations with lower smoking rates

Charge asks your advice on key decision points:

Data on which the IUR is based:
- Choice of sub-cohort
- Missing data (employment)

Quantitative assessment:
- Exposure-Response Modeling
  - Exposure metric
  - Model selection
- Adjustment for mesothelioma under ascertainment
- Derivation of combined unit risk for lung cancer and mesothelioma mortality
- Smoking as a potential confounder

Additional Literature

➢ **Supports EPA's finding that pleural thickening is observed in the low exposure range.**

Association Between Cumulative Fiber Exposure and Respiratory Outcomes Among Libby Vermiculite Workers *(Larson et al., JOEM, 2012)*

Radiographic Evidence of Non-occupational Asbestos Exposure from Processing Libby Vermiculite in Minneapolis Minnesota *(Alexander, et al., EHP, 2011)*

Modeling community asbestos exposure near a vermiculite processing facility: Impact of human activities on cumulative exposure *(Adgate et al., Journal of Exposure Science and Environmental Epidemiology (2011) 21, 529–535)*

Additional Literature

- **Supports EPA's finding that pleural plaques may contribute to observations of restrictive lung function deficits.**

Do asbestos-related pleural plaques on HRCT scans cause restrictive impairment in the absence of pulmonary fibrosis? {Clin et al., 2011, Thorax 2011 Nov;66(11):985-91}

Radiographic Abnormalities and Spirometry Results in a Cohort Exposed to Libby Amphibole. Larson et al., 2009-abstract Am J Respir Crit Care Med 179;2009:A5894. {Full publication upcoming}

Additional Literature

- **Supports EPA's focus sub-cohort that minimizes exposure measurement error.**

A meta-analysis of asbestos and lung cancer: Is better quality exposure assessment associated with steeper slopes of the exposure-response relationships? {Lenters et al. 2011, Env. Health Perspectives, Nov;119(11):1547-55.}

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Thank You

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- Department of Health and Human Services (ATSDR, NIEHS, and NIOSH)
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- Council on Environmental Quality